

AMENDMENTS TO THE CLAIMS

Please amend claims 40-42 as follows:

Claim 1 (Previously presented) A compound of Formula (I):

E^{CP}-A

(I)

or a pharmaceutically acceptable salt form thereof, wherein;

E^{CP} is an enzyme cleavable peptide conjugated to A and selected from:

Cap- Paa -Xa2 -Gly - Xp1 - Laa -;
Cap- Xa2 - Gly - Xp1 - Laa -;
Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Laa -;
Cap- Xa2 - Gly - Xp1 - Xp2 - Laa -;
Cap- Gly - Xp1 - Xp2 - Laa -;
Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa -;
Cap- Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa -;
Cap- Gly - Xp1 - Xp2 - Xp3 - Laa -;

Cap- Paa - Xa2 - Sar - Xp1 - Laa -;
Cap- Xa2 - Sar - Xp1 - Laa -;
Cap- Paa - Xa2 - Sar - Xp1 - Xp2 - Laa -;
Cap- Xa2 - Sar - Xp1 - Xp2 - Laa -;
Cap- Sar - Xp1 - Xp2 - Laa -;
Cap- Paa - Xa2 - Sar - Xp1 - Xp2 - Xp3 - Laa -;
Cap- Xa2 - Sar - Xp1 - Xp2 - Xp3 - Laa -; and
Cap- Sar - Xp1 - Xp2 - Xp3 - Laa -;

Paa is a Pro, Hyp, Aze, homo-Pro, Chg, Fph, Npa, Tzc, or proline mimetic;

Xa2 is an natural amino acid;

Xp1 is an amino acid wherein -Gly-Xp1- or -Sar-Xp1- form a bond cleavable by a matrixin;

Xp2 is an amino acid;

Xp3 is an amino acid;

Laa is an amino acid selected from Leu, Ile, Nle, β -homo-Leu, Hol, Hos, Ala, β -Ala, Cha, Cba, Cta, 4-pyridyl-Ala, 3-pyridyl-Ala, 2-pyridyl-Ala, Gly, Abu, Aib, Iva, Nva, Ahx, Aph, Amh, Phe, Bip, Glu, Arg, Trp, Tyr, O-(C₁-C₄ alkyl)-Tyr, O-(phenyl(C₁-C₄ alkyl))-Tyr, (C₃-C₈ alkyl)-Gly, and aminoalkyl carboxylic acid;

Cap is an N-terminus group selected from R-; Xa4-; and R-Xa4-;

Xa4- is an amino acid;

R is an amino capping group;

and

A is an antineoplastic agent;

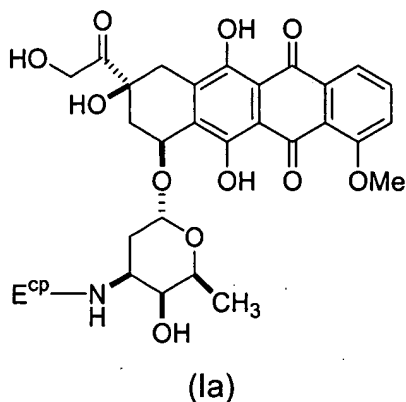
with the following provisos:

- a) Cap is not hydrogen;
- b) Cap is not a polyhydroxyalkanoyl;
- c) Cap is not a non-natural amino acid or succinyl;
- d) Cap is not benzyloxycarbonyl (Cbz);
- e) E^{CP} does not comprise a dipeptide linkage selected from -Tyr-Ser-; -Tyr-Thr-; -Phe-Ser-; -Gln-Ser-; -Gln-Thr-, and -Asn-Ser; and
- f) E^{CP} is not -Gly-Gly-Arg-Leu- (SEQ ID NO: 4),
E^{CP} is not -Gly-Val-Phe-Arg- (SEQ ID NO: 5),
E^{CP} is not -Ala-Pro-Gly-Leu- (SEQ ID NO: 6),
E^{CP} is not 2-thienylalanine-Gly-Ala-Leu- ,
E^{CP} is not 2-naphthylalanine -Gly-Ala-Leu- , or
E^{CP} is not -Gly-Leu-Gly-Leu- (SEQ ID NO: 7).

Claim 2 (ORIGINAL) A compound of Claim 1 wherein A is doxorubicin, a doxorubicin derivative, or a doxorubicin analogue.

Claim 3 (ORIGINAL) A compound of Claim 2 wherein A is doxorubicin.

Claim 4 (Previously presented) A compound of Claim 3 of Formula (Ia):



or a pharmaceutically acceptable salt form thereof, wherein;

E^{cp} is an enzyme cleavable peptide selected from:

- Cap- Paa - Xa2 - Gly - Xp1 - Laa -;
- Cap- Xa2 - Gly - Xp1 - Laa -;
- Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Laa -;
- Cap- Xa2 - Gly - Xp1 - Xp2 - Laa -;
- Cap- Gly - Xp1 - Xp2 - Laa -;
- Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa -;
- Cap- Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa -;
- Cap- Gly - Xp1 - Xp2 - Xp3 - Laa -;

- Cap- Paa - Xa2 - Sar - Xp1 - Laa -;
- Cap- Xa2 - Sar - Xp1 - Laa -;
- Cap- Paa - Xa2 - Sar - Xp1 - Xp2 - Laa -;
- Cap- Xa2 - Sar - Xp1 - Xp2 - Laa -;
- Cap- Sar - Xp1 - Xp2 - Laa -;
- Cap- Paa - Xa2 - Sar - Xp1 - Xp2 - Xp3 - Laa -;
- Cap- Xa2 - Sar - Xp1 - Xp2 - Xp3 - Laa -; and
- Cap- Sar - Xp1 - Xp2 - Xp3 - Laa -;

Paa is a Pro, Hyp, Aze, homo-Pro, Chg, Fph, Npa, Tzc, or proline mimetic;

Xa2 is an amino acid;

Xp1 is an amino acid wherein -Gly-Xp1- or -Sar-Xp1- form a bond cleavable by a matrixin;

Xp2 is an amino acid;

Xp3 is an amino acid;

Laa is an amino acid selected from Leu, Ile, Nle, β -homo-Leu, Hol, Hos, Ala, β -Ala, Cha, Cba, Cta, 4-pyridyl-Ala, 3-pyridyl-Ala, 2-pyridyl-Ala, Gly, Abu, Aib, Iva, Nva, Ahx, Aph, Amh, Phe, Bip, Glu, Arg, Trp, Tyr, O-(C₁-C₄ alkyl)-Tyr, O-(phenyl(C₁-C₄ alkyl))-Tyr, (C₃-C₈ alkyl)-Gly, and aminoalkyl carboxylic acid;

Cap is an N-terminus group selected from R-; Xa4-; and R-Xa4-;

Xa4- is an amino acid;

R is selected from: H₃CC(=O)-;

HOC(=O)-(CH₂)_vC(=O)-,

wherein v is 1, 2, 3, 4, 5, or 6;

H₃CO-(CH₂CH₂O)_t-CH₂C(=O)-,

HO₂CCH₂O-(CH₂CH₂O)_t-CH₂C(=O)-,

H₂N-(CH₂CH₂O)_t-CH₂C(=O)-, and

H₃CC(=O)HN-(CH₂CH₂O)_t-CH₂C(=O)-,

wherein t is 1, 2, 3, or 4;

R¹-C(=O)-;

R¹-S(=O)₂-;

R¹-NHC(=O)-;

R^{1a}-CH₂C(=O)-;

proline substituted with -OR³;

C₁-C₄ alkyl substituted with 0-1 R⁴; and

2-carboxyphenyl-C(=O)-;

R¹ is C₃-C₆ cycloalkyl substituted with 0, 1, or 2 substituents selected from -OH, methoxy and -CO₂H;

5-6 membered heterocycle; said heterocycle being saturated, partially saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S; said heterocycle optionally substituted with 1 or 2 -OH, methoxy or -CO₂H;

phenyl substituted with 0, 1, or 2 substituents selected from -OH, methoxy and -CO₂H; or

C₁-C₆ alkyl substituted with 0-4 R^{1a};

R^{1a} is -OH, C₁-C₃ alkyl, C₁-C₄ alkoxy, -CO₂H, -N(CH₂CH₂)₂N-R², -SO₃H;

C₃-C₆ cycloalkyl substituted with 0, 1, or 2 substituents selected from methoxy and -OH;

5-6 membered heterocycle; said heterocycle being saturated, partially saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S; said heterocycle optionally substituted with 1 or 2 -OH; or

phenyl substituted with 0, 1, or 2 substituents selected from methoxy and -OH;

R² is -H, H₂N(C₂-C₄ alkyl)-, acetyl(H)N(C₂-C₄ alkyl)-, or acetyl;

R³ is -H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, phenyl, or benzyl;

R⁴ is -OH, C₁-C₃ alkyl, C₁-C₄ alkoxy, -CO₂H, -N(CH₂CH₂)₂N-R²;

C₃-C₆ cycloalkyl substituted with 0, 1, or 2 substituents selected from methoxy and -OH;

5-6 membered heterocycle; said heterocycle being saturated, partially saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S; said heterocycle optionally substituted with 1 or 2 -OH; or

C₆-C₁₀ carbocycle substituted with 0, 1, or 2 substituents selected from methoxy and -OH.

Claim 5 (Previously presented) A compound of Claim 4 of Formula (Ia), or a pharmaceutically acceptable salt form thereof, wherein;

E^{CP} is an enzyme cleavable peptide selected from:

Cap- Paa - Xa2 - Gly - Xp1 - Laa -;
Cap- Xa2 - Gly - Xp1 - Laa -;
Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Laa -;
Cap- Xa2 - Gly - Xp1 - Xp2 - Laa -;
Cap- Gly - Xp1 - Xp2 - Laa -;
Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa -;
Cap- Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa -; and
Cap- Gly - Xp1 - Xp2 - Xp3 - Laa -;

Paa is a Pro, Hyp, Aze, homo-Pro, Chg, Fph, Npa, Tzc, or proline mimetic;

Xa2 is an amino acid;

Xp1 is an amino acid wherein -Gly-Xp1- forms a bond cleavable by a matrixin;

Xp2 is an amino acid;

Xp3 is an amino acid;

Laa is an amino acid selected from Leu, Ile, Nle, β -homo-Leu, Hol, Hos, Ala, β -Ala, Cha, Cba, Cta, 4-pyridyl-Ala, Abu, Aib, Iva, Nva, Phe, Bip, Tyr, and O-benzyl-Tyr; and

Cap is an N-terminus group selected from R-; Xa4-; and R-Xa4-;

Xa4- is an amino acid;

R is selected from: H₃CC(=O)-;

HOC(=O)-(CH₂)_vC(=O)-,

wherein v is 1, 2, 3, or 4;

H₃CO-(CH₂CH₂O)_t-CH₂C(=O)-,

HO₂CCH₂O-(CH₂CH₂O)_t-CH₂C(=O)-,

H₂N-(CH₂CH₂O)_t-CH₂C(=O)-, and

H₃CC(=O)HN-(CH₂CH₂O)_t-CH₂C(=O)-,

wherein t is 1, 2, or 3;

$R^1-C(=O)-$;
 $R^1-S(=O)_2-$;
 $R^1-NHC(=O)-$;
 $R^{1a}-CH_2C(=O)-$;
 proline substituted with $-OR^3$;
 C_1-C_4 alkyl substituted with 0-1 R^4 ;
 $HO_3SCH_2CH(NH_2)C(=O)-$; and
 2-carboxyphenyl- $C(=O)-$;

R^1 is C_3-C_6 cycloalkyl substituted with 0, 1, or 2 substituents selected from
 $-OH$, methoxy and $-CO_2H$;

5-6 membered heterocycle; said heterocycle being saturated, partially
 saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4
 heteroatoms selected from N, O, and S; said heterocycle optionally
 substituted with 1 or 2 $-OH$, methoxy or $-CO_2H$;

phenyl substituted with 0, 1, or 2 substituents selected from $-OH$, methoxy
 and $-CO_2H$; or

C_1-C_6 alkyl substituted with 0-4 R^{1a} ;

R^{1a} is $-OH$, C_1-C_3 alkyl, C_1-C_4 alkoxy, $-CO_2H$, $-N(CH_2CH_2)_2N-R^2$, $-SO_3H$;

C_3-C_6 cycloalkyl substituted with 0, 1, or 2 substituents selected from
 methoxy and $-OH$;

5-6 membered heterocycle; said heterocycle being saturated, partially
 saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4
 heteroatoms selected from N, O, and S; said heterocycle optionally
 substituted with 1 or 2 $-OH$; or

phenyl substituted with 0, 1, or 2 substituents selected from methoxy
 and $-OH$;

R^2 is $-H$, $H_2N(C_2-C_4 \text{ alkyl})-$, acetyl(H) $N(C_2-C_4 \text{ alkyl})-$, or acetyl;

R^3 is $-H$, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, phenyl, or benzyl;

R⁴ is -OH, C₁-C₃ alkyl, C₁-C₄ alkoxy, -CO₂H, -N(CH₂CH₂)₂N-R² ;

C₃-C₆ cycloalkyl substituted with 0, 1, or 2 substituents selected from methoxy and -OH;

5-6 membered heterocycle; said heterocycle being saturated, partially saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S; said heterocycle optionally substituted with 1 or 2 -OH; or

C₆-C₁₀ carbocycle substituted with 0, 1, or 2 substituents selected from methoxy and -OH.

Claim 6 (ORIGINAL) The compound of Claim 5, wherein -Gly-Xp1- forms a bond cleavable by the matrixin selected from MMP-2, MMP-9, and MMP-14.

Claim 7 (ORIGINAL) The compound of Claim 5, wherein -Gly-Xp1- forms a bond cleavable by the matrixin selected from MMP-2 and MMP-9.

Claim 8 (ORIGINAL) The compound of Claim 5, wherein -Gly-Xp1- forms a bond cleavable by the matrixin MMP-14.

Claim 9 (ORIGINAL) The compound of Claim 5, wherein -Gly-Xp1- forms a bond cleavable by MMP-2, MMP-9, and MMP-14.

Claim 10 (Previously presented) A compound of Claim 5 of Formula (Ia), or a pharmaceutically acceptable salt form thereof, wherein;

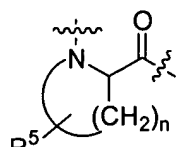
E^{CP} is an enzyme cleavable peptide selected from:

Cap- Paa - Xa2 - Gly - Xp1 - Laa - ;
Cap- Xa2 - Gly - Xp1 - Laa - ;
Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Laa - ;
Cap- Xa2 - Gly - Xp1 - Xp2 - Laa - ;
Cap- Gly - Xp1 - Xp2 - Laa - ;
Cap- Paa - Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa - ;
Cap- Xa2 - Gly - Xp1 - Xp2 - Xp3 - Laa - ; and

Cap- Gly - Xp1 - Xp2 - Xp3 - Laa -;

wherein -Gly-Xp1- forms a bond cleavable by a matrixin;

Paa is a Pro, Hyp, Aze, homo-Pro, Chg, Fph, Npa, Tzc, or proline mimetic of

formula: ; wherein R⁵ is selected from H, halogen, C₁-C₆ alkyl, -OH, C₁-C₆ alkoxy, and benzyloxy; and n is 2, 3, 4, or 5;

Xa2 is an amino acid selected from

Hof, Leu, His, Arg, Gln, Ile, Val, Lys, (R)-Leu, Orn, β-Ala, γ-Abu, Cha, Chg, Dap, Cit, N-methyl-Leu, valerolactam, N,N-dimethyl-Lys, 4-aza-Phe, morpholinylpropyl-Gly, N-methylpiperazinepropyl-Gly, 4-aza-Hof, Ala, Asn, Asp, Aze, Cys, Glu, Gly, Hyp, Irg, Met, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Cya, Hca, and Spa;

Xp1 is an amino acid selected from Hof; Leu; Bip; Phe; nor-Leu; Tha; Phg; Val;

Glu; Asn; Ser; Ala; homo-Tyr; Aze; 4-aza-Hof; O-(3-pyridyl)-Tyr;

O-(4-pyridyl)-Tyr; O-benzyl-Tyr; O-benzyl-Thr; O-benzyl-Ser;

O-methyl-Ser; O-allyl-Ser; 4-nitro-Hof; N-methyl-Leu;

O-(4-pyridylmethyl)-Tyr; 4-hydroxy-phenyl-Gly; phenylpropyl-Gly; styryl-Ala, and 2Nal;

Xp2 is an amino acid selected from Tyr; Ala; Ser; Leu; Gln; Val; Glu, His; Lys;

Arg; Orn; Aze; Hof; homo-Tyr; Cit; 4-aza-Phe; N,N-dimethyl-Lys; Dab; Dap;

Asn, Asp, Aze, Cha, Cys, Gly, Hyp, Ile, Irg, Met, Phe, Phe(4-fluoro), Pro,

Sar, Thr, Trp, Cya, Hca, Spa, morpholinylpropyl-Gly; O-(4-pyridylmethyl)-

Tyr; and N-methylpiperazinepropyl-Gly;

Xp3 is an amino acid selected from Tyr, Ala, Ser, Leu, Hof, Arg, Asn, Asp, Aze, Cha, Cys, Dpa, Gln, Glu, Gly, His, Hyp, Ile, Irg, Lys, Met, Orn, Phe, Phe(4-fluoro), Pro, Sar, Thr, Trp, and Val;

Laa is an amino acid selected from Leu, Ile, Nle, β -homo-Leu, Hol, Hos, Ala, β -Ala, Cha, Cba, Cta, 4-pyridyl-Ala, Abu, Aib, Iva, Nva, and Phe;

Cap is an N-terminus group selected from R-; Xa4-; and R-Xa4-;

Xa4- is an amino acid selected from Gly, Pro, γ -Glu, Dmg, Ala, Arg, Asn, Asp, β -Asp, Aze, Cha, Cys, Dpa, Gln, Glu, His, Hyp, Ile, Irg, Leu, Lys, Met, Orn, Phe, Sar, Ser, Thr, Trp, Tyr, and Val;

R is selected from: $\text{H}_3\text{CC}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{HO}_2\text{CCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{HNCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{HNCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{C}(\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{HNCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{C}(\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{C}(\text{O})-$;

$\text{O}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{CH}_2\text{NHC}(\text{O})-$;

$\text{HO}_2\text{CCH}_2\text{C}(\text{CO}_2\text{H})(\text{OH})\text{CH}_2\text{C}(=\text{O})-$;

$\text{HO}_2\text{CCH}_2\text{C}(\text{CH}_3)(\text{OH})\text{CH}_2\text{C}(=\text{O})-$;

2-carboxycyclohexyl- $\text{C}(=\text{O})-$;

2-carboxycyclopentyl-C(=O)-;
carbobenzyloxy;
4-methoxy-benzenesulfonyl;
cyclopropylcarbonyl;
cyclobutylcarbonyl;
3-pyridinecarbonyl;
2-pyrazinecarbonyl;
tetrazoleacetyl;
pivaloyl;
methoxyacetyl;
hydroxyproline; and
4-(2-(5,6,7,8-tetrahydronaphthenyl))butyl.

Claim 11 (ORIGINAL) The compound of Claim 10, wherein -Gly-Xp1- forms a bond cleavable by the matrixin selected from MMP-2, MMP-9, and MMP-14.

Claim 12 (ORIGINAL) The compound of Claim 10, wherein -Gly-Xp1- forms a bond cleavable by the matrixin selected from MMP-2 and MMP-9.

Claim 13 (ORIGINAL) The compound of Claim 10, wherein -Gly-Xp1- forms a bond cleavable by the matrixin MMP-14.

Claim 14 (ORIGINAL) The compound of Claim 10, wherein -Gly-Xp1- forms a bond cleavable by MMP-2 , MMP-9, and MMP-14.

Claim 15 (Previously presented) A compound of Formula (Ia), or a pharmaceutically acceptable salt form thereof, wherein;

E^{CP} is an enzyme cleavable peptide selected from:

Cap- Paa - Xa2 - Gly - Leu - Laa -;
Cap- Paa - Xa2 - Gly - Hof - Laa -;
Cap- Xa2 - Gly - Leu - Laa -;
Cap- Xa2 - Gly - Hof - Laa -;

Cap- Paa - Xa2 - Gly - Leu - Xp2 - Laa -;
 Cap- Paa - Xa2 - Gly - Hof - Xp2 - Laa -;
 Cap- Xa2 - Gly - Leu - Xp2 - Laa -;
 Cap- Xa2 - Gly - Hof - Xp2 - Laa -;
 Cap- Gly - Leu - Xp2 - Laa -; and
 Cap- Gly - Hof - Xp2 - Laa -;

wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by a matrixin;

Paa is a Pro, Hyp, Aze, homo-Pro, or Npa;

Xa2 is an amino acid selected from

Hof, Leu, His, Arg, Gln, Ile, Val, Lys, (R)-Leu, Orn, β -Ala, γ -Abu, Cha, Chg, Dap, Cit, N-methyl-Leu, valerolactam, N,N-dimethyl-Lys, 4-aza-Phe, morpholinylpropyl-Gly, N-methylpiperazinepropyl-Gly, 4-aza-Hof, Ala, Asn, Asp, Aze, Cys, Glu, Gly, Hyp, Irg, Met, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, Tyr, Cya, Hca, and Spa;

Xp2 is an amino acid selected from Tyr; Ala; Ser; Leu; Gln; Val; Glu, His; Lys; Arg; Orn; Aze; Hof; homo-Tyr; Cit; 4-aza-Phe; N,N-dimethyl-Lys; Dab; Dap; Asn, Asp, Aze, Cha, Cys, Gly, Hyp, Ile, Irg, Met, Phe, Phe(4-fluoro), Pro, Sar, Thr, Trp, Cya, Hca, Spa, morpholinylpropyl-Gly; O-(4-pyridylmethyl)-Tyr; and N-methylpiperazinepropyl-Gly;

Laa is an amino acid selected from Leu, Cha, Nle, and Hol;

Cap is an N-terminus group selected from R-; Xa4-; and R-Xa4-;

Xa4- is an amino acid selected from Gly, Pro, γ -Glu, and Dmg;

R is selected from: $\text{H}_3\text{CC}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{C(=O)-}$;
 $\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C(=O)-}$;
 $\text{HO}_2\text{CCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C(=O)-}$;
 $\text{H}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{C(=O)-}$;
 $\text{H}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C(=O)-}$;
 $\text{H}_3\text{CC(=O)HNCH}_2\text{CH}_2\text{OCH}_2\text{C(=O)-}$;
 $\text{H}_3\text{CC(=O)HNCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C(=O)-}$;
 $\text{H}_2\text{NCH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2)_2\text{NCH}_2\text{C(O)-}$;
 $\text{H}_3\text{CC(=O)HNCH}_2\text{CH}_2\text{N(CH}_2\text{CH}_2)_2\text{NCH}_2\text{C(O)-}$;
 $\text{H}_3\text{CC(=O)N(CH}_2\text{CH}_2)_2\text{NCH}_2\text{C(O)-}$;
 $\text{O(CH}_2\text{CH}_2)_2\text{NCH}_2\text{CH}_2\text{NHC(O)-}$;
 $\text{HO}_2\text{CCH}_2\text{C(CO}_2\text{H)(OH)CH}_2\text{C(=O)-}$;
 $\text{HO}_2\text{CCH}_2\text{C(CH}_3\text{)(OH)CH}_2\text{C(=O)-}$;
 2-carboxycyclohexyl-C(=O)-;
 2-carboxycyclopentyl-C(=O)-;
 carbobenzyloxy;
 4-methoxy-benzenesulfonyl;
 cyclopropylcarbonyl;
 cyclobutylcarbonyl;
 3-pyridinecarbonyl;
 2-pyrazinecarbonyl;
 tetrazoleacetyl;
 pivaloyl;
 methoxyacetyl;
 hydroxyproline; and
 4-(2-(5,6,7,8-tetrahydronaphthenyl))butyl.

Claim 16 (ORIGINAL) The compound of Claim 15, wherein -Gly-Leu- and -Gly-Hof-
 form a bond cleavable by the matrixin selected from MMP-2, MMP-9, and MMP-14.

Claim 17 (ORIGINAL) The compound of Claim 15, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin selected from MMP-2 and MMP-9.

Claim 18 (ORIGINAL) The compound of Claim 15, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin MMP-14.

Claim 19 (ORIGINAL) The compound of Claim 15, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by MMP-2, MMP-9, and MMP-14.

Claim 20 (Previously presented) A compound of Claim 15 of Formula (Ia), or a pharmaceutically acceptable salt form thereof, wherein;

E^{CP} is an enzyme cleavable peptide selected from:

Cap- Paa - Xa2 - Gly - Leu - Leu -;
Cap- Paa - Xa2 - Gly - Leu - Cha -;
Cap- Paa - Xa2 - Gly - Leu - Nle -;
Cap- Paa - Xa2 - Gly - Leu - Hol -;
Cap- Paa - Xa2 - Gly - Hof - Leu -;
Cap- Paa - Xa2 - Gly - Hof - Cha -;
Cap- Paa - Xa2 - Gly - Hof - Nle -;
Cap- Paa - Xa2 - Gly - Hof - Hol -;
Cap- Paa - Xa2 - Gly - Leu - Xp2 - Leu -;
Cap- Paa - Xa2 - Gly - Leu - Xp2 - Cha -;
Cap- Paa - Xa2 - Gly - Leu - Xp2 - Nle -;
Cap- Paa - Xa2 - Gly - Leu - Xp2 - Hol -;
Cap- Paa - Xa2 - Gly - Hof - Xp2 - Leu -;
Cap- Paa - Xa2 - Gly - Hof - Xp2 - Cha -;
Cap- Paa - Xa2 - Gly - Hof - Xp2 - Nle -; and
Cap- Paa - Xa2 - Gly - Hof - Xp2 - Hol -;

wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by a matrixin;

Paa is a Pro, Hyp, Aze, homo-Pro, or Npa;

Xa2 is an amino acid selected from

Hof, Leu, His, Arg, Gln, Ile, Val, Lys, (R)-Leu, Orn, β -Ala, γ -Abu, Cha, Chg, Dap, Cit, N-methyl-Leu, valerolactam, N,N-dimethyl-Lys, 4-aza-Phe, morpholinylpropyl-Gly, N-methylpiperazinepropyl-Gly, 4-aza-Hof, Ala, Asn, Asp, Aze, Cys, Glu, Gly, Hyp, Irg, Met, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, and Tyr;

Xp2 is an amino acid selected from Tyr; Ala; Ser; Leu; Gln; Val; Glu, His; Lys; Arg; Orn; Aze; Hof; homo-Tyr; Cit; 4-aza-Phe; N,N-dimethyl-Lys; Dab; Dap; Asn, Asp, Aze, Cha, Cys, Gly, Hyp, Ile, Irg, Met, Phe, Phe(4-fluoro), Pro, Sar, Thr, Trp; morpholinylpropyl-Gly; O-(4-pyridylmethyl)-Tyr; and N-methylpiperazinepropyl-Gly;

Cap is an N-terminus group selected from R-; Xa4-; and R-Xa4-;

Xa4- is an amino acid selected from Gly, Pro, γ -Glu, and Dmg;

R is selected from: $\text{H}_3\text{CC}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

2-carboxycyclohexyl- $\text{C}(=\text{O})-$;

2-carboxycyclopentyl- $\text{C}(=\text{O})-$; and

tetrazoleacetyl.

Claim 21 (ORIGINAL) The compound of Claim 20, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin selected from MMP-2, MMP-9, and MMP-14.

Claim 22 (ORIGINAL) The compound of Claim 20, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin selected from MMP-2 and MMP-9.

Claim 23 (ORIGINAL) The compound of Claim 20, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin MMP-14.

Claim 24 (ORIGINAL) The compound of Claim 20, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by MMP-2, MMP-9, and MMP-14.

Claim 25 (Previously presented) A compound of Claim 15 of Formula (Ia), or a pharmaceutically acceptable salt form thereof, wherein;

E^{CP} is an enzyme cleavable peptide selected from:

Cap- Xa2 - Gly - Leu - Leu -;
Cap- Xa2 - Gly - Leu - Cha -;
Cap- Xa2 - Gly - Leu - Nle -;
Cap- Xa2 - Gly - Leu - Hol -;
Cap- Xa2 - Gly - Hof - Leu -;
Cap- Xa2 - Gly - Hof - Cha -;
Cap- Xa2 - Gly - Hof - Nle -;
Cap- Xa2 - Gly - Hof - Hol -;
Cap- Xa2 - Gly - Leu - Xp2 - Leu -;
Cap- Xa2 - Gly - Leu - Xp2 - Cha -;
Cap- Xa2 - Gly - Leu - Xp2 - Nle -;
Cap- Xa2 - Gly - Leu - Xp2 - Hol -;
Cap- Xa2 - Gly - Hof - Xp2 - Leu -;
Cap- Xa2 - Gly - Hof - Xp2 - Cha -;
Cap- Xa2 - Gly - Hof - Xp2 - Nle -; and
Cap- Xa2 - Gly - Hof - Xp2 - Hol -;

wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by a matrixin;

Xa2 is an amino acid selected from

Hof, Leu, His, Arg, Gln, Ile, Val, Lys, (R)-Leu, Orn, β -Ala, γ -Abu, Cha, Chg, Dap, Cit, N-methyl-Leu, valerolactam, N,N-dimethyl-Lys, 4-aza-Phe, morpholinylpropyl-Gly, N-methylpiperazinepropyl-Gly, 4-aza-Hof, Ala, Asn,

Asp, Aze, Cys, Glu, Gly, Hyp, Irg, Met, Phe, Phe(4-fluoro), Pro, Sar, Ser, Thr, Trp, and Tyr;

Xp2 is an amino acid selected from Tyr; Ala; Ser; Leu; Gln; Val; Glu; His; Lys; Arg; Orn; Aze; Hof; homo-Tyr; Cit; 4-aza-Phe; N,N-dimethyl-Lys; Dab; Dap; Asn, Asp, Aze, Cha, Cys, Gly, Hyp, Ile, Irg, Met, Phe, Phe(4-fluoro), Pro, Sar, Thr, Trp; morpholinylpropyl-Gly; O-(4-pyridylmethyl)-Tyr; and N-methylpiperazinepropyl-Gly;

Cap is an N-terminus group selected from R-; Xa4-; and R-Xa4-;

Xa4- is an amino acid selected from Gly, Pro, γ -Glu, and Dmg;

R is selected from: $\text{H}_3\text{CC}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

2-carboxycyclohexyl- $\text{C}(=\text{O})-$;

2-carboxycyclopentyl- $\text{C}(=\text{O})-$; and

tetrazoleacetyl.

Claim 26 (ORIGINAL) The compound of Claim 25, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin selected from MMP-2, MMP-9, and MMP-14.

Claim 27 (ORIGINAL) The compound of Claim 25, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin selected from MMP-2 and MMP-9.

Claim 28 (ORIGINAL) The compound of Claim 25, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by the matrixin MMP-14.

Claim 29 (ORIGINAL) The compound of Claim 25, wherein -Gly-Leu- and -Gly-Hof- form a bond cleavable by MMP-2, MMP-9, and MMP-14.

Claims 30-34 (CANCELLED)

Claim 35 (ORIGINAL). A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

Claim 36 (Previously presented) A method of treating a mammal afflicted with a cancer comprising administering to a mammal afflicted with a cancer a therapeutically effective amount of a compound of Claim 1.

Claim 37 (ORIGINAL). The method of Claim 36, wherein the cancer is a breast, ovarian, brain, stomach, lung, colon, prostate or liver cancer or wherein the cancer is a leukemia, lymphoma, carcinoma, sarcoma, or melanoma.

Claim 38. (ORIGINAL) A method of delivering a compound to the cells of a mammal afflicted with a cancer comprising contacting the cells of a mammal afflicted with a cancer with a compound of Claim 1, wherein the contacting is in the presence of a peptidase comprising a matrixin.

Claim 39 (ORIGINAL). The method of Claim 38, wherein the cancer is a breast, ovarian, brain, stomach, lung, colon, prostate or liver cancer or wherein the cancer is a leukemia, lymphoma, carcinoma, sarcoma, or melanoma.

Claim 40 (Currently amended) A compound of Claim 4 of Formula (I), or a pharmaceutically acceptable salt form thereof, wherein;
E^{CP} is an enzyme cleavable peptide selected from:



~~(γ -E-P-L-G is provided as SEQ ID NO: 52)~~

R is selected from: $\text{H}_3\text{CC}(=\text{O})-$;

$\text{HOC}(=\text{O})-(\text{CH}_2)_v\text{C}(=\text{O})-$;

wherein v is 1, 2, 3, 4, 5, or 6;

$\text{H}_3\text{CO}-(\text{CH}_2\text{CH}_2\text{O})_t\text{CH}_2\text{C}(=\text{O})-$;

$\text{HO}_2\text{CCH}_2\text{O}-(\text{CH}_2\text{CH}_2\text{O})_t\text{CH}_2\text{C}(=\text{O})-$;

$\text{H}_2\text{N}-(\text{CH}_2\text{CH}_2\text{O})_t\text{CH}_2\text{C}(=\text{O})-$; and

$\text{H}_3\text{CC}(=\text{O})\text{HN}-(\text{CH}_2\text{CH}_2\text{O})_t\text{CH}_2\text{C}(=\text{O})-$;

wherein t is 1, 2, 3, or 4;

$\text{R}^1\text{-C}(=\text{O})-$;

$\text{R}^1\text{-S}(=\text{O})_2-$;

$\text{R}^1\text{-NHC}(=\text{O})-$;

$\text{R}^{1a}\text{-CH}_2\text{C}(=\text{O})-$;

proline substituted with $-\text{OR}^3$;

$\text{C}_1\text{-C}_4$ alkyl substituted with 0-1 R^4 ; and

2-carboxyphenyl- $\text{C}(=\text{O})-$;

R^1 is $\text{C}_3\text{-C}_6$ cycloalkyl substituted with 0, 1, or 2 substituents selected from $-\text{OH}$, methoxy and $-\text{CO}_2\text{H}$;

5-6 membered heterocycle; said heterocycle being saturated, partially saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S; said heterocycle optionally substituted with 1 or 2 $-\text{OH}$, methoxy or $-\text{CO}_2\text{H}$;

phenyl substituted with 0, 1, or 2 substituents selected from $-\text{OH}$, methoxy and $-\text{CO}_2\text{H}$; or

$\text{C}_1\text{-C}_6$ alkyl substituted with 0-4 R^{1a} ;

R^{1a} is $-\text{OH}$, $\text{C}_1\text{-C}_3$ alkyl, $\text{C}_1\text{-C}_4$ alkoxy, $-\text{CO}_2\text{H}$, $-\text{N}(\text{CH}_2\text{CH}_2)_2\text{N-R}^2$, $-\text{SO}_3\text{H}$;

C₃-C₆ cycloalkyl substituted with 0, 1, or 2 substituents selected from methoxy and -OH;

5-6 membered heterocycle; said heterocycle being saturated, partially saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S; said heterocycle optionally substituted with 1 or 2 -OH; or

phenyl substituted with 0, 1, or 2 substituents selected from methoxy and -OH;

R² is -H, H₂N(C₂-C₄ alkyl)-, acetyl(H)N(C₂-C₄ alkyl)-, or acetyl;

R³ is -H, C₁-C₄ alkyl, C₃-C₆ cycloalkyl, phenyl, or benzyl;

R⁴ is -OH, C₁-C₃ alkyl, C₁-C₄ alkoxy, -CO₂H, -N(CH₂CH₂)₂N-R² ;

C₃-C₆ cycloalkyl substituted with 0, 1, or 2 substituents selected from methoxy and -OH;

5-6 membered heterocycle; said heterocycle being saturated, partially saturated or unsaturated; said heterocycle containing 1, 2, 3, or 4 heteroatoms selected from N, O, and S; said heterocycle optionally substituted with 1 or 2 -OH; or

C₆-C₁₀ carbocycle substituted with 0, 1, or 2 substituents selected from methoxy and -OH.

Claim 41 (NEW) A compound of Claim 40 of Formula (I), or a pharmaceutically acceptable salt form thereof, wherein;

E^{CP} is an enzyme cleavable peptide selected from:

R-γ-E -P-L-G-(O-benzyl-S)-Y-L-;

(SEQ ID NO: 186)

~~(γ-E -P-L-G is provided as SEQ ID NO: 52)~~

R is selected from: $\text{H}_3\text{CC}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{HOC}(=\text{O})\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{COCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{HO}_2\text{CCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_2\text{NCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{HNCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{HNCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OCH}_2\text{C}(=\text{O})-$;

$\text{H}_2\text{NCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{C}(\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{HNCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{C}(\text{O})-$;

$\text{H}_3\text{CC}(=\text{O})\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{C}(\text{O})-$;

$\text{O}(\text{CH}_2\text{CH}_2)_2\text{NCH}_2\text{CH}_2\text{NHC}(\text{O})-$;

$\text{HO}_2\text{CCH}_2\text{C}(\text{CO}_2\text{H})(\text{OH})\text{CH}_2\text{C}(=\text{O})-$;

$\text{HO}_2\text{CCH}_2\text{C}(\text{CH}_3)(\text{OH})\text{CH}_2\text{C}(=\text{O})-$;

2-carboxycyclohexyl- $\text{C}(=\text{O})-$;

2-carboxycyclopentyl- $\text{C}(=\text{O})-$;

carbobenzyloxy;

4-methoxy-benzenesulfonyl;

cyclopropylcarbonyl;

cyclobutylcarbonyl;

3-pyridinecarbonyl;

2-pyrazinecarbonyl;

tetrazoleacetyl;

pivaloyl;

methoxyacetyl;

hydroxyproline; and

4-(2-(5,6,7,8-tetrahydronaphthenyl))butyl.

Claim 42 (NEW) A compound of Claim 40 of Formula (I), or a pharmaceutically acceptable salt form thereof, wherein;

E^{CP} is an enzyme cleavable peptide selected from:

R-γ-E -P-L-G-(O-benzyl-S)-Y-L-;

(SEQ ID NO: 186)

~~(γ-E-P-L-G is provided as SEQ ID NO: 52)~~

R is selected from: H₃CC(=O)-;

HOC(=O)CH₂CH₂C(=O)-;

HOC(=O)CH₂CH₂CH₂C(=O)-;

HOC(=O)CH₂CH₂CH₂CH₂C(=O)-;

H₃COCH₂CH₂OCH₂C(=O)-;

H₃COCH₂CH₂OCH₂CH₂OCH₂C(=O)-; and

tetrazoleacetyl.